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Quick Pulse

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TERCICA'S INCRELEX GROWTH HORMONE

The FDA is reviewing Tercica's Increlex (mecasermin injection) for the long-term treatment of growth failure in children with a severe form of primary IGF-1 deficiency (Primary IGFD). Insulin-like Growth Factor (IGF-1) is the principal hormone necessary for statural growth (height). Primary IGFD is a disease characterized by lack of IGF-1 production in the presence of normal or elevated levels of endogenous growth hormone.

Five pediatric endocrinologists were asked about growth hormones in general and Increlex in particular. Doctors generally agreed that it is extremely uncommon to see a child with height standard deviation scores of -3 and normal growth hormone. A California doctor *(considered the premier expert on this topic)* said, "A definition of -3 is extremely rare, and -2 happens in 3% of children. -3 happens in about one in a thousand children, and of those, I'd say half would be growth hormone deficient. Being that short is very unusual, but if you are, you have a problem with one of your hormones." A Maryland doctor said, "It's very rare (to see a child with a height deviation score of -3) – less than 1% of children. Most of the children who have true growth hormone resistance syndrome have either an altered growth hormone gene or an altered growth hormone receptor gene, and because there need to be both copies of the gene to be altered, it's usually seen in children who are products of consanguineous unions. Because consanguineous practice is rare in this country, we hardly see it at all. There are more children like this in the Middle East and South America."

Sources also agreed that IGF-1 is well understood. One doctor said, "IGF-1 is routinely measured. We have a lot of experience with measuring IGF-1, and it is typically lower in shorter patients. IGF-1 is also low in people with idiopathic short stature." Another said, "IGF-1 is well understood. It is a marker of growth hormone effect, and it is typically low in growth hormone deficiency, but it is also modulated by nutritional status, so it would be very low in a starvation state such as anorexia nervosa."

Doctors found it harder to agree on what percentage of patients seen for growth disorder are ***not*** candidates for growth hormone. One said, "It's hard to say. For patients with -3, they're all candidates for growth hormone, and at least 10% don't respond to that. Not everyone responds to IGF-1, and it's difficult to say how many." Another physician said, "It depends on how you define this. There is probably a very, very small percentage of children who would respond to IGF-1 that would not respond to growth hormone."

Several companies have worked on IGF-1 in the past, but they stopped development because of side effects. A source offered this background and perspective on IGF-1:

- "At the same time, Insmed was working on a related product – IGF alone and in combination with IGF-Bp3 – essentially competing products similar to IGF-1. Insmed bought the rights from Pharmacia (now Pfizer), and both of these companies have initiated development of IGF-1 simultaneously for growth disorders, including a new disease entity they have sort of provoked, called IGF-1 deficiency, which is similar to a condition called idiopathic short stature – short people without growth hormone deficiency.

- "Growth hormone is a commonly used drug for improvement of growth in children and represents a billion dollar industry worldwide. These small companies are hoping that IGF-1 can acquire a niche for those individuals who don't respond to growth hormone but who respond to IGF-1."

- "Today, growth hormone is the only thing we have. When IGF-1 is available, it will be a completely new paradigm, and we'll have to define how we use it. There will be pressure to use each company's drug."

Will doctors use IGF-1? Yes, but most likely not first-line. Rather, doctors are generally very interested in Increlex for use as a second-line drug in certain patients. One source said, "I have high expectations for selective patients those with low IGF-1 and lack of response to growth hormones. It's a very potent molecule that normally is produced in the body. It represents a very important development target." Another source said, "Most patients first go on growth hormones. How long is the question. One way is to use the IGF-1 generation test, treat someone for a week with growth hormone, and see if the IGF level goes up. If it doesn't, try IGF-1. We have decades of experience with growth hormones and very little with IGF, so initially people will start with growth hormone." Another physician said, "It depends on how you define this. There is probably a very small percentage of children who would respond to IGF-1 who would not respond to growth hormone. IGF-1 has some additional potential risks that growth hormone doesn't have, such as hypoglycemia." A third doctor said, "IGF-1 has great potential for the small percentage of patients who do not respond to growth hormone."

Physicians familiar with Increlex and willing to talk about it were optimistic about the drug and predicted the FDA will approve it. A California doctor said, "The initial data for a few hundred patients with severe IGF deficiency because of growth hormone insensitivity show that IGF-1 is indeed effective in improving growth, with few side effects." Another said, "Insmed submitted its drug for approval a few months earlier than Tercica and got word that the FDA would grant it a review. Tercica submitted a few months ago and is expecting a letter from the FDA that will give the same kind of review. The two products are slightly different, but they represent a class, and I think the FDA has learned to recognize the significance of class in medication."

However, questions continue about potential, though unseen, side effects, including cancer, retinopathy, hypoglycemia, and cardiac toxicity. A source said, "The side effects reported have been relatively minor and rare and include local injection site effects, pain in joints, and occasional low blood sugar."

- **Cancer.** No increased risk of cancer has been proven, but the clinical trial experience with IGF-1 is limited. Yet, an expert said he believes the FDA is unlikely to block development of this drug without any data that the cancer side effect actually occurs. He explained, "(It has been thought that) individuals with naturally high IGF levels have a higher incidence of cancer than those with low levels, but that hasn't been proven to be the case."

- **Retinopathy.** An expert said, "The retinopathy issue is the worsening of eye disease in diabetics. There was a concern there, but I don't think it will come up in non-diabetics, so it's not really an issue."

- **Hypoglycemia.** A source said, "IGF-1 has an insulin-like effect, but with proper use these are all manageable, and I suspect the FDA will approve ***both*** products (Insmed's and Tercica's)."

- **Cardiac toxicity.** A doctor said, "There were concerns about IGF-1 when it first came out, questions about whether it could cause cardiac arrest when given intravenously. I'm not sure how those issues have been dealt with."

Reimbursement and insurance coverage are potential problems. A source said, "Insurance companies are in the business of not paying. Right now, Increlex is not approved, but when it is approved for the indications, we'll have a good case to ask insurance companies to pay for it. However, it's always an uphill battle." Another said, "Being that it's difficult for growth hormone (to get reimbursement), my guess is that insurance companies aren't going to jump on the IGF-1 bandwagon either. It's impossible to know unless it's FDA-approved for specific indications."

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